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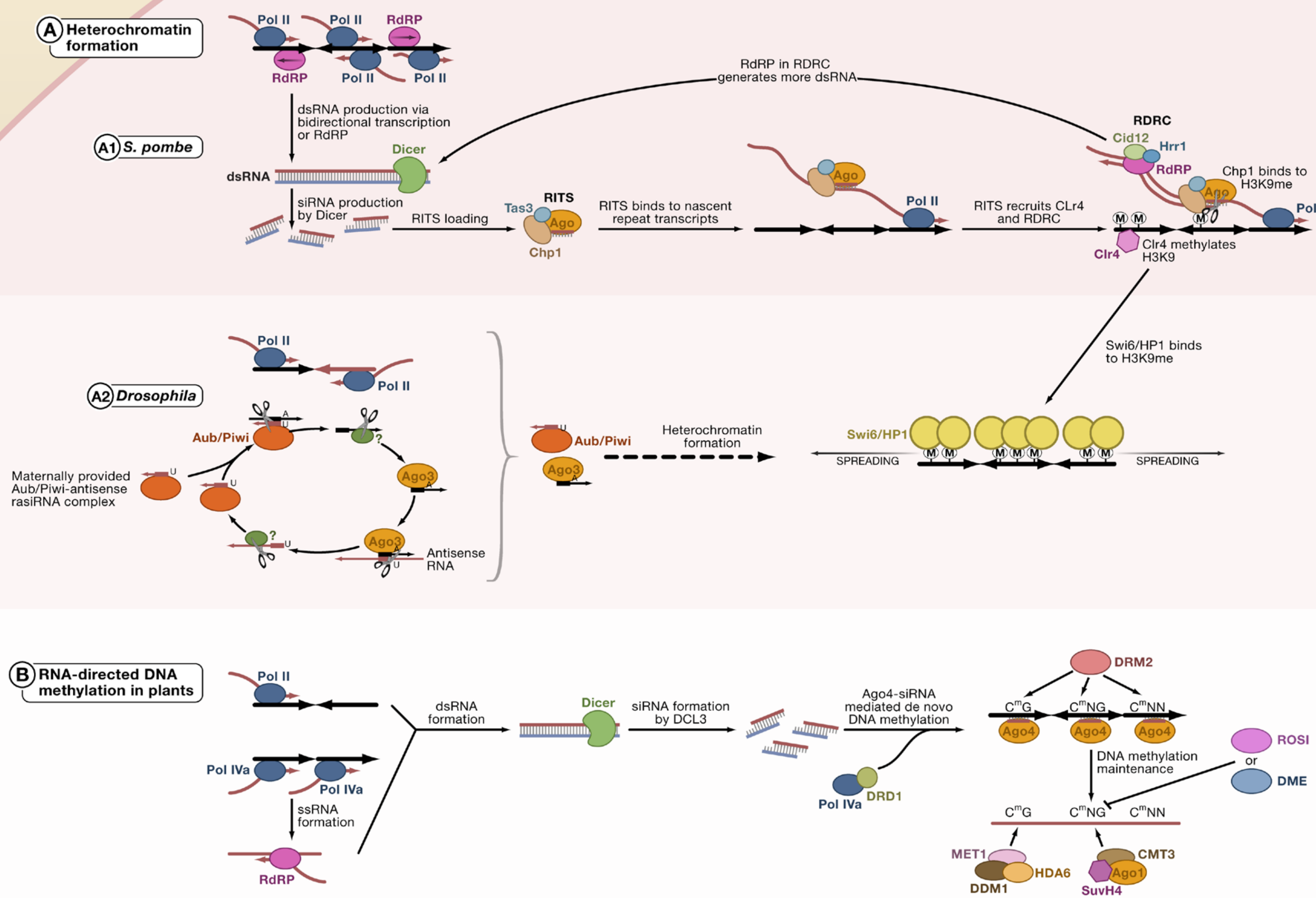
SnapShot: Small RNA-Mediated Epigenetic Modifications

Yanxia Bei, Sigal Pressman, and Richard Carthew
Department of Biochemistry, Molecular Biology and Cell Biology, Northwestern University, Evanston, IL 60208, USA



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See online version for legend, abbreviations, and references.

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(A) Heterochromatin Formation

Although heterochromatin formation occurs in the nucleus, it is not clear in which cellular compartment the events leading up to small RNA-directed heterochromatin formation occur.

A1: Heterochromatin Formation in *Schizosaccharomyces pombe*. DNA repeats produce double-stranded (ds)RNAs through bidirectional transcription or RNA-dependent RNA synthesis. dsRNAs are cut into small-interfering (si)RNAs that are loaded into an RNA-induced transcriptional silencing complex (RITS) that consists of Ago, Tas3, an *S. pombe* specific protein, and Chp1, a chromodomain containing protein. RITS finds the DNA repeats through siRNA base pairing with the nascent transcript and recruits the RNA-directed RNA polymerase complex (RDRC) and Clr4, a histone methyltransferase that methylates histone H3 at lysine 9 (H3K9me). RdRP in RDRC uses the Ago-cut nascent RNA as template to synthesize more dsRNA, which in turn will be cut into siRNAs to reinforce heterochromatin formation. Chp1 in the RITS complex binds to H3K9me, resulting in stable interaction of RITS and heterochromatic DNA. H3K9me also binds to another chromodomain protein, Swi6, an HP1 homolog, leading to the spreading of heterochromatin.

A2: Heterochromatin Formation in *Drosophila*. Repeat associated small interfering RNAs (rasiRNAs) are produced in a Dicer independent, Aub/Piwi-Ago3 "ping-pong" mechanism. Aub/Piwi associates with antisense rasiRNAs with a preference for a U at 5′ end, whereas Ago associates with sense-strand derived rasiRNA with a preference to an A at nucleotide 10. Aub/Piwi-rasiRNA complex binds to sense-strand RNA via a 10 nucleotide (nt) complementary sequence. Aub/Piwi cleaves sense-strand RNA, producing sense rasiRNA precursor. A yet-to-be-identified nuclease (?) generates the sense rasiRNAs that associate with Ago3. In turn, Ago3-sense siRNA binds to antisense RNA and generates more antisense rasiRNAs. In this ping-pong model, the initial Aub/Piwi-rasiRNA complex is maternally deposited. The resulting rasiRNA complexes initiate heterochromatin formation (dotted arrow line). As in yeast, H3K9me binds to a HP1 protein, leading to the spreading of heterochromatin. A similar mechanism has been reported in mammals.

(B) RNA-Directed DNA Methylation in Plants

These events happen primarily in the nucleus. This model is based on studies in *Arabidopsis thaliana*. Inverted DNA repeats generate dsRNAs via Pol II transcription, whereas tandem DNA repeats initially produce, by Pol IVa, single-stranded (ss)RNAs that are then converted into dsRNAs by RDR2. These dsRNAs from either source are cut by DCL3 into 24 nt siRNAs, which associate with Ago4. siRNA-Ago4 complexes together with Pol IVb and DRD1, an SNF2-like chromatin remodeling protein, initiate de vovo cytosine methylation by DRM2, a DNA methyltransferase. DDM1, another SNF2-like chromatin remodeling factor, MT1, and HDA6 are required to maintain CG methylation; whereas CMT3, SVUH4, and Ago1 are required for CNG methylation maintenance. Two DNA glycosylases, ROS1 and DME, can demethylate cytosine within CNG content.

Abbreviations

Aub, Aubergine; Ago, Argonaute; Chp1, chromodomain protein 1; Cid12, caffeine-induced death protein; Clr4, cryptic loci regulator 4; CMT3, chromomethylase 3; DCL3, Dicer-like protein 3; dsRNA, double-stranded RNA; DDM1, defective in DNA methylation 1; DME, DEMETER; DRD1, defective in RNA-directed DNA methylation 1; DRM2, domain rearranged methyltransferase; H3K9, histone H3 lysine 9; H3K9me, methylated histone H3 lysine 9; HDA6, histone deacetylase 6; HP1, heterochromatin protein 1; Hrr1, helicase required for RNAi-mediated heterochromatin assembly; MET1, DNA methyltransferase 1; Pol II, RNA polymerase II; Pol IVa/Pol IVb, RNA polymerase IV isoform a/b; rasiRNA, repeat associated small-interfering RNA; RdRP/RDR, RNA dependant RNA polymerase; RDRC, RNA-directed RNA polymerase complex; RITS, RNA-induced transcriptional silencing complex; ROS1, repressor of silencing 1; siRNA, small-interfering RNA; SuvH4, suppressor of variegation homolog 4; Swi6, mating type switching mutant 6; Tas3, targeting complex subunit 3.

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